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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/270,983	HAY ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 57-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,7 and 57-69* is/are rejected.

7)☒ Claim(s) *4,6,70 and 71* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants amendment canceling claim 8 amending claim 1 and adding new claims 59 to 71, in the paper of 1/12/2004, is acknowledged.

Claims 1-7 and 59-71 are at issue and are present for examination.

Applicants' arguments filed on 1/12/2004, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

Claims 4, 6, 70 and 71 are objected to because of the following informalities: Claims 4, 6, 70 and 71 are objected to because they depend from rejected claims 3, 67 and 69.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 59-66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to claims 1-4, 7 and 58. In response to this rejection applicants have amended claim1 and added new claims 59-71 and traverse the rejection as it applies to the newly amended claims.

Applicants note that the rejection is relevant only to new claims 59 to 66, which are directed to a fusion protein, which comprises a reporter polypeptide linked to a linker polypeptide, etc...

Applicants submit that the skilled artisan, viewing the subject application, would have known applicants were in possession of the claimed fusion proteins comprising an enzyme reporter polypeptide, more specifically the specification discloses that a repressor polypeptide can be a signal peptide, which directs secretion of a fusion protein of the invention into an extracellular space or external environment or can be for example a nuclear localization sequence or mitochondrial localization signal and that it is well known that enzymes have specific requirements for activity including for example pH, ionic strength, co-factor requirements and access to an appropriate substrate. Applicants further support applicants position by submitting that for example a kinase reporter polypeptide that is linked to a signal peptide, would be exported from a cell and therefore would not have access to an intracellular substrate, thus exhibiting reduced activity.

Applicants are reminded that the claimed genus of fusion proteins is directed to those comprising a repressor which represses the enzymatic activity of the reporter

polypeptide by conferring a specific localization **in a cell** such that the reporter polypeptide has reduced enzymatic activity. Regardless, applicants argument is not found persuasive for the following. Applicant is reminded that the referred to hypothetical kinase would only have reduced activity for an intracellularly isolated substrate, however its activity for additional substrates such as those which occur extracellularly would increase. While it is well known that enzymes have a specific requirement for activity, including for example pH, ionic strength, co-factor requirements and access to an appropriate substrate, applicants have not adequately described such reporter enzymes and the above relative conditions as they relate to a repressor polypeptide that represses through cellular localization and thus those claims include a reporter polypeptide which is any possible enzyme continue to not be sufficiently described.

Thus claims 59-66 remain rejected under 112 first paragraph based on a lack of description for a fusion protein comprising a repressor polypeptide that represses the activity of the reporter polypeptide by conferring specific localization in a cell such that the reporter polypeptide has reduced activity, wherein said reporter is any enzyme.

As no predictability of structure is apparent for the claimed genus and given the lack of disclosed species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 59-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for those fusion proteins comprising a reporter polypeptide and a repressor polypeptide that represses the activity of the reporter polypeptide by conferring a specific localization in the cell such that the attached reporter has reduced activity, wherein said reporter polypeptide is a transcriptional activator, does not reasonably provide enablement for a fusion protein comprising a reporter polypeptide and a repressor polypeptide that represses the activity of the reporter polypeptide by conferring a specific localization in the cell such that the attached reporter has reduced activity, wherein said reporter polypeptide is a any enzyme. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applied to claims 1-4, 7 and 58. In response to this rejection applicants have amended claim1 and added new claims 59-71 and traverse the rejection as it applies to the newly amended claims.

As above, applicants note that the rejection is relevant only to the subject matter of new claims 59 to 66, which are directed to a fusion protein, which comprises a reporter polypeptide linked to a linker polypeptide, etc...

Applicants submit that methods of making fusion proteins, including methods of making fusion proteins that comprise a heterologous cell localization domain were well known in the art at the time the subject application was filed and as such undue experimentation would not have been required to make a fusion protein, comprising for example, a kinase linked to a signal peptide such that the kinase would be exported from a cell in which it otherwise has activity. Applicants argue that the skilled artisan would have known that the enzyme reporter of such a fusion protein would have reduced activity outside of a cell due, to lack of access of intracellular substrate etc...

Applicants are reminded that the claimed genus of fusion proteins is directed to those comprising a repressor which represses the enzymatic activity of the reporter polypeptide by conferring a specific localization **in a cell** such that the reporter polypeptide has reduced enzymatic activity. Technically one might argue that applicants submitted example is not encompassed by the claimed genus. Regardless, applicants argument is not found persuasive because applicants disclosure of one species of enzyme, a kinase, many of which would not be sufficiently repressed through the described mechanism, is not representative nor gives adequate guidance for the claimed genus of fusion proteins which comprises any enzyme reporter and any repressor which represses the enzymatic activity of the reporter polypeptide by conferring a specific localization in a cell such that the reporter polypeptide has reduced enzymatic activity.

Applicants have not given guidance as to how to make such a fusion protein, such that it comprises a enzyme reporter which is repressed by a repressor which does

so through by specific localization in a cell such that the reporter polypeptide has reduced enzymatic activity.

Because of this lack of guidance, and the extended experimentation that would be required, it would require undue experimentation for one skilled in the art to make the claimed fusion proteins.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1- 3, 5, 57-61, 64 and 67-69 are rejected under 35 U.S.C. 102(b) as being anticipated by Sakai et al. (Cell, Vol 85, pp 1037-1046, 1996).

The rejection was stated in the previous office action and repeated below for applicants convenience.

Sakai et al. teach a H-Ras-SREP-2 fusion protein comprising a NH2-terminal segment of approximately 500 amino acids, which projects into the cytosol and comprises a transcription factor (reporter polypeptide), linked to a middle segment which comprises a helical hairpin membrane anchor (repressor polypeptide) consisting

of two transmembrane helices followed by an approximate 500 amino acid in length carboxy-terminal segment. Further the taught fusion protein comprises a protease cleavage site near the first transmembrane domain, which upon cleavage releases the NH2-terminal segment which then enters the nucleus and activates transcription by binding to a 10 bp sterol regulatory element. Sakai et al. further teach that in addition to sterol-regulated proteolysis, SREBP-2 can be cleaved in a sterol-independent manner by CPP-32 and Mch-3, two cysteine proteases that are activated during programmed cell death.

In response to this rejection applicants have amended claim 1 added new claims 59-71 and traverse the rejection as it applies to the newly amended claims. Newly added claims 59-61, 64 and 67-69 are included in the rejection for the reasons previously stated for claims 1-3, 5, 57 and 58.

Applicants traverse this rejection on the following basis. Applicants point out that the NH2-terminal segment of the fusion protein of Sakai et al. consists of the H-Ras sequence (see Figure 3A, page 1040) and that H-Ras is not a transcription factor per se, though it can activate transcription via a signal transduction pathway, being a GTP-binding protein. Applicants further submit that upon cleavage the H-Ras segment localized to the cytosol, not to the nucleus and that Sakai et al. do not appear to report whether transcriptional activity was increased in test cells. Thus based on the above, applicants submit that since H-Ras is not a transcription factor, Sakai et al. would not appear to be relevant to those claims directed to reporter proteins that are transcription factors, such as claims 5, 6, and 67 to 71, although applicants admit that because H-

Ras can be considered a transcriptional activator and has GTPase activity, it can be considered a reporter polypeptide encompassed within the subject matter of claims 1 to 4, 7 and 58 to 64.

As Sakai et al. is used to anticipate claims 1 to 4, 7 and 58 to 64, applicants submit that Sakai et al. do not teach or suggest a fusion protein of the invention because the SREP-2 portion of the fusion protein of Sakai et al. contains two protease cleavage sites, including a first cleavage site and a second cleavage site that operate as per the model presented in Figure 1 of Sakai et al. Based on applicants characterization, applicants conclude that Sakai et al. do not teach or suggest a fusion protein containing a protease cleavage site, which when cleaved results in increased activity of a reporter polypeptide and therefore do not anticipate the claimed fusion proteins.

Both of applicants above arguments are not found persuasive for the following reasons.

First, with respect to applicants argument that Sakai et al. does not teach or suggest claims 5, 6, and 67 to 71 because H-Ras is not a transcription factor per se, it is agreed that H-Ras is not a transcription factor per se, however, the fusion protein which Sakai et al. teaches which is relevant to those claims wherein the reporter is a transcription factor is not the fusion protein which comprises H-Ras, but rather the wildtype sterol regulatory element binding protein (SREBP-2) itself which as taught by Sakai et al. is a transcription factor attached to the endoplasmic reticulum, wherein the NH2-segment activates transcription and is connected to membranes via a hairpin

anchor formed by two transmembrane sequences and a short lumenal loop, wherein said transmembrane sequence comprises a protease cleavage site (See abstract, Figure 1 and supporting test).

Second, with respect to applicants argument that Sakai et al. do not teach or suggest a fusion protein of the invention because the SREP-2 portion of the fusion protein of Sakai et al. contains two protease cleavage sites, including a first cleavage site and a second cleavage site that operate as per the model presented in Figure 1 of Sakai et al., applicants is reminded that claims are drawn to the fusion protein comprising a linker polypeptide comprising a protease cleavage site, wherein upon cleavage of said linker polypeptide at said protease cleavage site, an increase in the transcriptional activity of said reporter can be detected. Cleavage at the protease cleavage site, (within the transmembrane) results in an increase in the transcriptional activity of said reporter polypeptide (NH2-segment transcription factor) which can be detected. Applicants claims do not necessitate that the claimed protein cannot contain more then one protease cleavage site, but merely that upon cleavage of said linker polypeptide at said protease cleavage site, an increase in the transcriptional activity of said reporter can be detected and the fusion proteins taught by Sakai et al. meet this limitation and thus anticipate claims 1- 3, 5, 57-61, 64 and 67-69.

Claims 1, 3, 5, 57-61, 64 and 67-69 are rejected under 35 U.S.C. 102(e) as being anticipated by Crabtree et al. (U.S. Patent No. 5,380,462).

The rejection was stated in the previous office action and repeated below for applicants convenience.

Crabtree et al. teach a number of chimeric proteins comprising at least one ligand-binding (or "receptor") domain fused to an additional "action" domain, wherein the chimeric proteins are derived from different sources not normally found together in nature. Crabtree et al. teach that the action domain may be a transcriptional activator (See column 13, lines 42-61) or additional regulatory systems such as protein kinase or phosphatase activities. Crabtree further teach that the chimeric protein may have an intracellular targeting domain which targets the chimeric protein to the plasma membrane (See column 12, lines 29-36 and Figure 18). While Crabtree et al. do not describe the specifically taught domains as per the instant inventors, (i.e. "repressor polypeptide", "reporter polypeptide" and "linker polypeptide") the chimeric proteins taught by Crabtree et al. anticipate the instantly claimed "fusion proteins".

In response to this rejection applicants have amended claim 1 and added new claims 59-71 and traverse the rejection as it applies to the newly amended claims. New claims 59-61, 64 and 67-69 are included in the rejection for the reasons previously stated for claims 1-3, 5, 57 and 58.

Applicants submit that Crabtree et al. generally teach chimeric proteins that oligomerize, including for example, as homodimers or heterodimers, due to the linking action of bivalent ligands. Applicants further submit that the chimeric proteins of Crabtree et al. are active only upon oligomerization and as such when considered in its

entirety, the Crabtree et al. reference does not appear to be particularly relevant to the claimed compositions.

Applicants argument is not found persuasive on the basis that it is not a necessary limitation of the claimed fusion proteins that they not form an oligomer, and regardless of whether oligomerization is necessary in order to become active is irrelevant to the currently rejected claims. As above applicants is reminded that the claims are drawn to the fusion protein comprising a linker polypeptide comprising a protease cleavage site, wherein upon cleavage of said linker polypeptide at said protease cleavage site, an increase in the transcriptional activity of said reporter can be detected. Applicants claims make no reference to the necessity to form or not form an oligomer.

Applicants further point out that the chimeric proteins of Crabtree et al. are readily distinguishable from the claimed fusion proteins because for example the fusion proteins of Crabtree et al. are designed to localize to a cellular compartment in which they have activity, in contrast to the claimed fusion protein which have a reduced activity due to the specific localization in a cell conferred by the repressor domain.

Applicants argument is not found persuasive on the basis applicants appear to be focusing on but one embodiment of that taught and/or suggested by Crabtree et al. , referring to column 13, lines 43-45. Applicants is reminded that not all of the fusion proteins of Crabtree et al. are designed to localize to a cellular compartment in which they have activity, applicants attention is directed to Figure 18 and the supporting text (i.e. Example 4A, column 37, lines 42-60).

Applicants further point out that Crabtree et al. do not teach or suggest linking an action domain and a localization domain with a linker polypeptide containing a protease cleavage site. This argument is not found persuasive because the fusion proteins taught by Crabtree et al. inherently have an action domain and a localization domain with a linker polypeptide containing a protease cleavage site. Further applicants attention is directed to column 25, lines 29-61 in which Crabtree et al. teach that various of the functionalities of the taught invention can be linked by peptides which comprise sites of cleavage by various proteases.

Thus claims 1, 3, 5, 57-61, 64 and 67-69 remain anticipated by Crabtree et al.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (571) 272-0930. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
3/22/2004